

Effect of early treatment with propranolol on left ventricular function four weeks after myocardial infarction

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SUMMARY Left ventricular function and exercise capacity were assessed in 79 patients randomised to receive intravenous and oral propranolol ($n=44$) or conventional therapy ($n=35$) within four hours of onset of their first myocardial infarction. Cineangiocardiology and exercise testing were performed four weeks after infarction to allow for maximum recovery of myocardial function. Left ventriculography showed no improvement in ejection fraction or preservation of regional contractile function in patients treated with propranolol compared with controls. A trend towards smaller end diastolic volumes was seen in the propranolol group (mean (SD) 151(42) ml) compared with controls (167(42) ml). Exercise duration and frequency of angina were not significantly different in the two groups. It is concluded that limitation of infarct size by propranolol does not lead to a significant improvement in ventricular systolic function, although left ventricular dilatation may be reduced. These findings are consistent with the known effect of early intravenous beta blockade which limits infarct size by preservation of subepicardial myocardium.

Infarct size, reflected by the degree of left ventricular dysfunction, is accepted as the major predictor of cardiac mortality after myocardial infarction. Limitation of infarct size with propranolol was first shown experimentally by Maroko and colleagues in 1971¹ and indirect indices of infarct size have been used in man to demonstrate a beneficial effect of beta blockers.²⁻⁴ The hypothesis, however, that limitation of infarct size would lead to improvement in ventricular function has been poorly evaluated in man. Pathophysiological observations suggest that treatment would be most effective if it were started early—within four hours of the onset of infarction.⁵ We have analysed late ventricular function and exercise capacity in a group of patients randomised to receive intravenous propranolol or conventional therapy within four hours of onset of their first infarction.

Patients and methods

Between May 1981 and March 1984 a randomised trial of intravenous propranolol versus no inter-

vention was conducted in 735 patients with suspected myocardial infarction.⁶ Entry to the trial was required within four hours of the onset of chest pain, which was of at least 30 minutes' duration and judged to be due to myocardial ischaemia. Exclusion criteria were asthma, significant cardiac failure, systolic blood pressure below 110 mm Hg, or heart rate below 60 beats per minute. Intravenous propranolol (0.1 mg/kg) was followed by an oral dose of up to 320 mg given over the next 27 hours, in divided doses of 40 mg. Individual doses were omitted when there was bradycardia of less than 50 beats per min or systolic blood pressure below 100 mm Hg, and treatment was discontinued if there was cardiac failure or atrioventricular block of greater than first degree. In the propranolol group there was a significant reduction in the incidence of ventricular fibrillation within the first 48 hours after infarction.⁶ There was no reduction in mortality and the frequency of heart block or use of diuretic therapy was similar in both groups.

Over the same period a subgroup of all male patients less than 60 years of age with no previous myocardial infarction who entered the trial from one hospital with cardiac catheterisation facilities was selected prospectively for investigation four weeks after their initial hospital admission. Patients who

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had had cardiac surgery were excluded. All patients selected had electrocardiographic evidence of abnormal Q waves (Q wave infarction) or serial ST segment and T wave changes without abnormal Q waves (non-Q wave infarction) and raised creatine kinase. The study was approved by the hospital ethics committee and all patients gave informed consent.

Patients were readmitted to hospital for exercise testing and angiocardiology four weeks after infarction. Exercise testing was performed on a treadmill at a constant speed of 2.5 miles (4 km) per hour at gradients of 0, 5, and 10 degrees for three minutes each and 15 degrees for six minutes. Exercise was stopped if significant angina or dyspnoea developed, and a 12 lead electrocardiogram was recorded immediately after exercise. Flat or downsloping ST segment depression of 1 mm was required as evidence for myocardial ischaemia.

Single plane left ventriculography and coronary angiography were carried out by the Judkins technique, left ventriculography being performed in the 40° right anterior oblique position. Left ventriculograms were recorded on 35 mm cine film at 50 frames per second. Cine film images were projected and the end diastolic and end systolic outlines were hand traced and subsequently digitised. Extrasystoles and post extrasystolic beats were excluded from the analysis. Ventricular volumes and ejection fraction were calculated by Simpson's rule with correction factors based on a comparison of radio-opaque left ventricular casts from postmortem hearts,⁷ and the indices were calculated according to body surface area. Experienced cardiac radiologists who were unaware of the randomisation group, assessed left ventricular contractility by subjective analysis of the movement of the cardiac silhouette in the right anterior oblique projection which was divided into five segments. Each segment was scored for contractility: normal 0, hypokinetic 1, akinetic 2, and dyskinetic 3, and the number from each segment was summed to give a contractility score (range 0 to 15).⁸ Calculation of the coronary arteriographic score⁹ was based both on the severity of the individual stenotic lesions and on the amount of left ventricular myocardium supplied by each involved vessel. This arteriographic score was expressed by a number in the range of 0–15; ≤5 was approximately equivalent to one vessel disease; 5–10 to two vessel disease; and > 10 to three vessel disease.

Data on clinical features together with results of angiocardiology and exercise testing were stored on a PDP11 minicomputer. Clinical and electrocardiographic variables were compared by means of the χ^2 test. No distribution of continuous variables was assumed, and accordingly comparison between groups was made by means of the non-parametric

Mann-Whitney U test with a two-tailed p-value. Results are expressed as mean (SD).

Results

Study group

Of the 735 patients admitted to the randomised trial, 407 developed myocardial infarction. Of these, 94 patients were enrolled at one hospital and met our inclusion criteria for subsequent investigation of sex (male), age less than 60 years, and no previous infarction. Fifty of these patients received intravenous propranolol, and 44 conventional treatment. Eight patients died in hospital or before investigation (three propranolol, five control). Patients with serious unrelated medical disorders were not regarded as suitable for investigation (three propranolol, three control) and one patient in the control group refused investigation. The clinical characteristics of the remaining patients, 44 in the propranolol and 35 in the control group, are listed in Table 1. Treated patients were older than controls (mean 52 *vs* 47 years, $p=0.004$), but the frequency of previous angina was similar in the two groups. Four patients in the control group and eight in the propranolol group were receiving beta blocker therapy before their infarction. Baseline heart rate and blood pressure before entry to the trial were similar in both groups. The mean time of administration of the first intravenous dose of propranolol was 2.8 hours from the onset of chest pain and was less than 4 hours in all patients. Heart rate fell from a mean of 79 beats per minute to 68 beats per minute within 10 minutes of administration of intravenous propranolol; this resembles the change observed in our previously reported trials in which a reduction of creatine kinase

Table 1 Clinical and electrocardiographic data on propranolol and control groups

	Propranolol (n = 44)	Control (n = 35)
Age in years (mean and range)	52 (35–59)	47 (32–59)
Previous angina 3 months' duration	12 (27%)	7 (20%)
Beta blocker therapy before entry	8 (18%)	4 (11%)
Baseline mean heart rate (SD)	79 (15)	79 (19)
Baseline mean blood pressure (mm Hg)	150/95	153/96
Electrocardiogram on entry:		
Normal	1 (2%)	3 (9%)
Abnormal Q waves	13 (30%)	10 (29%)
ST segment elevation	36 (82%)	22 (63%)
Primary ST depression	3 (7%)	5 (14%)
T wave inversion only	3 (7%)	5 (14%)
Time from onset of pain to trial entry (h (SD))	2.8 (0.7)	2.4 (1.0)
Final diagnosis:		
Anterior Q wave infarction	23 (52%)	15 (43%)
Inferior Q wave infarction	13 (30%)	12 (34%)
Non-Q wave infarction	8 (18%)	8 (23%)

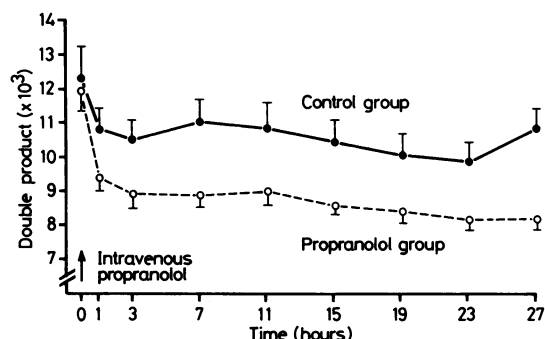


Fig. 1 Reduction of double product (systolic blood pressure \times heart rate) after intravenous and oral propranolol in the propranolol group compared with the control group. Means and standard errors are shown.

was shown in the propranolol group.²¹⁰ The lower double product (systolic blood pressure \times heart rate) achieved in the propranolol group is shown in Fig. 1. ST segment elevation was more common in the propranolol group on entry (82% *vs* 63%, $p=0.1$), and on discharge from hospital this group showed a higher proportion of completed anterior Q wave infarcts than did the control group (52% *vs* 43%, $p=NS$).

Exercise test

The protocol was completed by 24 and 22 patients of the control and propranolol groups respectively (p , not significant), while the mean exercise duration of patients not completing the protocol was 9(3) minutes in both groups. Similar numbers of patients in the control and propranolol groups developed angina during the exercise test (17 *vs* 15 patients) and ischaemic electrocardiographic changes after exercise (13 *vs* 14 patients). The peak mean heart rate was 141(26) beats per minute in the control group compared with 137(25) beats per minute in the propranolol group (p , not significant). Seven patients in the control group and nine in the propranolol group were on beta blockers at the time of exercise testing.

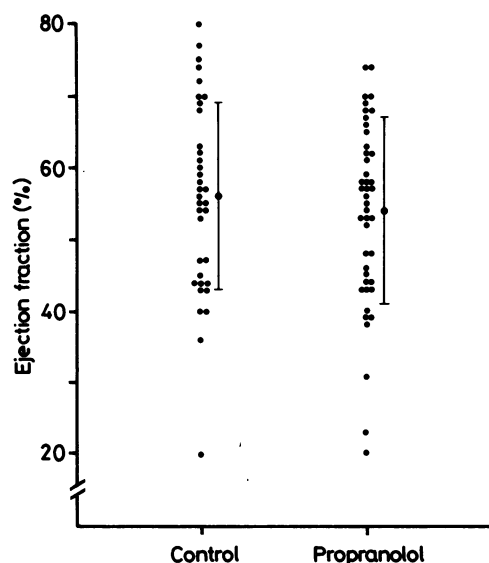


Fig. 2 Ejection fraction of individual patients 4 weeks after their first myocardial infarction in control ($n=35$) and propranolol ($n=44$) groups.

Cineangiocardiology

Group values for end diastolic volume, end systolic volume, ejection fraction, and contractility scores are shown in Table 2, while the ejection fractions and end diastolic volumes of individual patients are shown in Figs. 2 and 3. There was no significant difference for any of these variables between the propranolol and control groups. This result was unchanged after correction of ventricular volumes for body surface area. There was a trend towards smaller end diastolic volumes in the propranolol group (151 (42) ml *vs* 167(42) ml, $p=0.08$). In the total group of patients the contractility score correlated well with the ejection fraction ($r=0.78$).

Subgroup analysis based on the position and extent of infarction (Table 2) showed that all propranolol subgroups had lower mean end diastolic volumes than the control subgroups, although this

Table 2 Indices of left ventricular function for propranolol and control groups

	Propranolol				Control			
	EDV (ml)	ESV (ml)	EF (%)	Contractility score	EDV (ml)	ESV (ml)	EF (%)	Contractility score
Total group (P=44, C=35)	151 (42)	72 (35)	54 (13)	3.1 (2.1)	167 (42)	75 (34)	56 (13)	2.8 (1.8)
Anterior infarction (P=23, C=15)	161 (42)	85 (36)	48 (13)	4.2 (1.9)	170 (45)	81 (38)	53 (14)	3.5 (1.7)
Inferior infarction (P=13, C=12)	141 (47)	65 (32)	55 (9)	2.6 (1.6)	173 (25)	80 (26)	54 (12)	3.2 (1.8)
Non-Q wave infarction	140 (31)	48 (17)	66 (7)	0.7 (1.0)	150 (54)	57 (33)	64 (12)	1.2 (1.0)

P, propranolol; C, control; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction. Values are mean (SD).

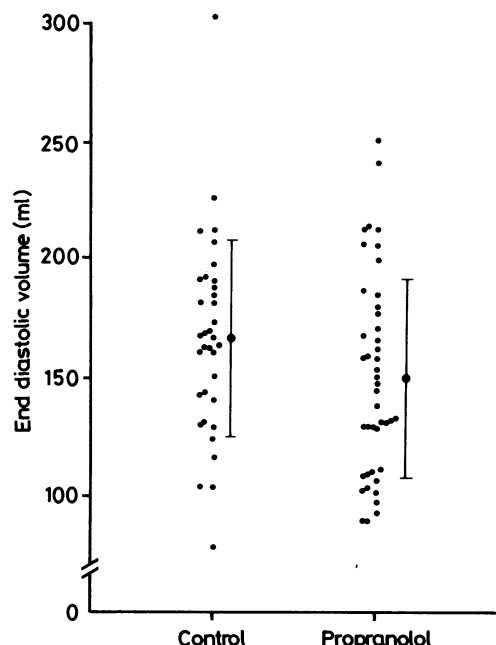


Fig. 3 End diastolic volumes of individual patients in control and propranolol groups. There is a non-significant trend to lower end diastolic volumes in the propranolol group ($2p=0.08$).

reached significance only with inferior Q wave infarcts (141(47) vs 173(25) ml, $p=0.04$). Despite early entry to the trial, when intervention may be of most benefit, 29% of all patients had abnormal Q waves in the area of infarction on entry (Table 1). These patients might have been least likely to benefit from intervention, since most of the eventual infarct size was likely to have already been reached. Reanalysis after exclusion of these cases, however, showed no benefit in the propranolol group.

The mean coronary arteriographic score was similar in both groups (propranolol 9.0(2.5), control 8.4(2.2)). Arteriography showed complete occlusion of the infarct related coronary artery in 76% of patients (propranolol 79%, control 74%). The coronary score of an occluded infarct related artery is a measure of the volume of myocardium distal to the occlusion, and according to our scoring system when it is divided by 15 it estimates the proportion of the left ventricle which has lost its primary blood supply. The mean score of the infarct related coronary artery of the control group was 4.6 (31% of the left ventricle), while that of the propranolol group was also 4.6, indicating that the volume of myocardium at risk from infarction was similar. Comparison of patients treated with propranolol or conventionally in whom incomplete occlusion of the infarct related artery was

found at coronary angiography showed no significant improvement of ventricular function in the propranolol group.

Discussion

There was no apparent significant difference in exercise duration or the frequency of angina between propranolol and control groups. End systolic volume, ejection fraction, and subjective assessment of the severity of regional dysfunction were also not significantly different in these groups. There was a trend to lower end diastolic volumes in the propranolol group which approached statistical significance.

The similarity of the groups at entry is clearly important to any conclusions drawn about the value of this intervention. The propranolol group was significantly older with a higher percentage of patients having electrocardiographic ST elevation on entry ($p=0.1$) and completed anterior Q wave infarction on discharge ($p=NS$). The extent of coronary artery disease and the size of the occluded infarct related vascular bed are important determinants of infarct size and these variables were similar in the two groups. There was, however, a wide variance for each index of ventricular function in both groups that was due to spontaneous variation in infarct size. Given the variance in this study, a sample of 107 patients in each group would have been necessary to detect a difference in ejection fraction of 5% at a significance level of $2p=0.05$ with a probability of 80%. No improvement in mean ejection fraction was seen in the propranolol group, however, suggesting that a larger study is unlikely to show a clinically significant improvement in ventricular systolic function.

We believe that ours is the first study to examine adequately the effect on left ventricular function of early intervention with intravenous beta blockers. The effect on ventricular function after infarction of delayed intervention with acebutolol has been reported¹¹; no significant improvement in late ejection fraction or ventricular volumes was seen when intravenous acebutolol was given six to 24 hours after the onset of chest pain. This protocol, however, was designed to prevent infarct extension rather than to limit infarct size by early intervention. We reported the results of angiocardiology in 28 patients enrolled in an earlier trial of propranolol,¹⁰ but the limited number of patients that we studied may have been responsible for the failure to show improvement in left ventricular function with propranolol.

Experimental and clinical evidence strongly suggests, however, that infarct size is limited after intra-

venous administration of beta blockers. Experimental evidence is based on reduction of the extent of infarction seen at necropsy,¹²⁻¹⁴ preservation of creatine kinase enzyme activity,¹⁵ and prevention of microvascular¹⁶ and mitochondrial¹⁷ injury. Creatine kinase release correlates strongly with anatomical infarct size measured at necropsy in patients who die from infarction,¹⁸⁻²⁰ and it also correlates reasonably well with subjective assessment of myocardial function assessed by cine-angiography after infarction⁸ and assessment of the percentage of abnormally contracting segments.²¹ We have previously shown a 20%–30% reduction in creatine kinase release when propranolol was given within four hours of the onset of chest pain,²¹⁰ and this result has been confirmed in further trials that assessed the effect of other beta blockers.³⁴ Important variables such as the maximal duration of chest pain and the propranolol regimen used in this study were identical to those in our previous studies. The reduction in double product after intravenous and oral propranolol was also similar, and, although a measurement of creatine kinase release was not repeated in this study, there is no reason to expect a result dissimilar to our previous studies. Vectorcardiographic analysis also correlates with extent of infarction determined experimentally in baboons,²² and preservation of QRS vector has been reported with timolol.⁴

A conclusion from the evidence cited above is that limitation of infarct size by 20%–30% with early administration of beta blockers should lead to improvement in ventricular function. This hypothesis has not previously been tested and is not supported by our results. Experimental evidence, however, suggests that limitation of infarct size by 20%–30% would not necessarily lead to a parallel improvement in myocardial function. Hearse and Yellon have addressed the controversy about the border zone of infarction and have suggested that a significant border zone does not exist at the edge of the developing infarction, but rather lies in the transmural plane between subepicardium and subendocardium.²³ Flow gradients in the transmural plane favouring the subepicardium occur after acute coronary artery ligation in dogs⁵²⁴ and it is the subepicardium which seems to be protected by treatment with propranolol.¹²¹⁵ A similar situation has been reported in man,²⁵ where the relation of infarct size to the vascular bed at risk was the result of variation in the transmural extent of necrosis and not the result of variation in the lateral zone of viable muscle, which was consistently narrow.

Preservation of subepicardial myocardium may not contribute to regional function. Sonomicrometry in normal myocardium of dogs has shown that the

inner half of the myocardium contributes approximately 70%–80% of the overall wall thickening,²⁶²⁷ so that the subepicardial myocardium may not contribute greatly to total wall thickening. Ellis *et al* recently reported on the correlation of infarct size with myocardial contractile function in dogs during coronary artery reperfusion.²⁸ Reduction by more than 40% of the transmural extent of infarction was necessary before there was a significant improvement in contractile function. Thus salvage of myocardium in the infarct zone to the degree seen with propranolol may not be sufficient to result in an improvement in ventricular systolic function.

It is conceivable, however, that preservation of subepicardium might splint the infarct zone and prevent infarct expansion.²⁹ This could limit the increase in end diastolic volume, and this would accord with the trend which we found in the present study. None the less the functional sequelae at best appear to be small and we consider it unlikely that beta blocker therapy will significantly reduce mortality from cardiogenic shock or cardiac failure. Improved myocardial preservation may result from the combination of treatment with beta blockers and reperfusion,³⁰ while maintaining the benefit of prevention of ventricular fibrillation.⁶

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